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# Comparison of Celox-A, ChitoFlex, WoundStat, and Combat Gauze Hemostatic Agents Versus Standard Gauze Dressing in Control of Hemorrhage in a Swine Model of Penetrating Trauma

Lanny F. Littlejohn, MD, John J. Devlin, MD, Sara S. Kircher, Robert Lueken, MD, Michael R. Melia, MD, and Andrew S. Johnson, MD

## Abstract

***Objectives:*** Uncontrolled hemorrhage remains one of the leading causes of trauma deaths and one of the most challenging problems facing emergency medical professionals. Several hemostatic agents have emerged as effective adjuncts in controlling extremity hemorrhage. However, a review of the current literature indicates that none of these agents have proven superior under all conditions and in all wound types. This study compared several hemostatic agents in a lethal penetrating groin wound model where the bleeding site could not be visualized.

***Methods:*** A complex groin injury with a small penetrating wound, followed by transection of the femoral vessels and 45 seconds of uncontrolled hemorrhage, was created in 80 swine. The animals were then randomized to five treatment groups (16 animals each). Group 1 was Celox-A (CA), group 2 was combat gauze (CG), group 3 was Chitoflex (CF), group 4 was WoundStat (WS), and group 5 was standard gauze (SG) dressing. Each agent was applied with 5 minutes of manual pressure. Hetastarch (500 mL) was infused over 30 minutes. Hemodynamic parameters were recorded over 180 minutes. Primary endpoints were attainment of initial hemostasis and incidence of rebleeding.

***Results:*** Overall, no difference was found among the agents with respect to initial hemostasis, rebleeding, and survival. Localizing effects among the granular agents, with and without delivery mechanisms, revealed that WS performed more poorly in initial hemostasis and survival when compared to CA.

From the Department of Emergency Medicine, Naval Medical Center, Portsmouth, VA.

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Supervising Editor: Robert T. Gerhardt, MD, MPH.

Address for correspondence and reprints: Lanny F. Littlejohn, MD; e-mail: lanny.littlejohn@med.navy.mil.

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***Conclusions:*** In this swine model of uncontrolled penetrating hemorrhage, SG dressing performed similarly to the hemostatic agents tested. This supports the concept that proper wound packing and pressure may be more important than the use of a hemostatic agent in small penetrating wounds with severe vascular trauma.

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Uncontrolled hemorrhage is the second leading cause of death in civilian trauma patients,[1,2] and the search for efficacious treatment in prehospital settings remains one of the most challenging problems facing emergency medical professionals. Particularly challenging are cases of extremity bleeding in a location not amenable to tourniquet placement, such as a small penetrating wound that severs the femoral artery proximal to where a tourniquet would be effective. With a better understanding of the role of hemostatic agents, dressings, and products designed to rapidly promote coagulation and arrest ongoing hemorrhage, these cases may represent preventable deaths.

In the prehospital phase, hemostatic agents can potentially reduce morbidity and mortality through the early control of hemorrhage. Early control of hemorrhage is crucial. Even with adequate resuscitation, significant blood loss leads to hypothermia, coagulopathy, acidosis, and late ''second-hit'' mortality that occurs through the development of sepsis and multiple organ failure.[3] When hospital resuscitation includes blood transfusion, mortality increases independent of shock severity.[4] Therefore, it is important to determine the efficacy of competing hemostatic agents in the control of early hemorrhage.

Hemostatic agents vary in mechanism of action, from activating the intrinsic pathway of coagulation using kaolin (combat gauze [CG]), to adsorbing fluid to form a malleable clay (WoundStat [WS]), or by cross-linking red blood cells to form a mucoadhesive barrier with chitosan (Chitoflex [CF] or Celox-A [CA]). Hemostatic agent form factors also differ, from granular agents (WS, CA), to rolled gauze (CG) or flexible rolled bandage (CF), which may ultimately affect utility in various wound types. While retrospective human studies have shown efficacy of hemostatic agents over simple gauze dressings in both military[5,6] and civilian settings,[7] no hemostatic agent has unambiguously emerged as superior in either the laboratory or the clinical settings.

Animal studies have explored the effects of hemostatic agents on large cavitary injury models with direct visualization of the bleeding site.[8–18] However, in both civilian and combat trauma, gunshot wounds commonly result in an isolated penetrating extremity injury. Further, anecdotal reports from deployed combat medics and corpsmen indicate that some hemostatic agents may be less effective on smaller, linear-tract wounds with severe vessel injury, such as injury from bullets or fragments from improvised explosive devices.[19] Although less severe, similar injuries are seen in civilian trauma.[20] Furthermore, some wound models lack the severity to threaten mortality sufficiently to fully challenge hemostatic agents.

Accordingly, the present study used a model specifically designed to simulate the ragged, lacerated muscle of the cavity associated with high-velocity projectile tracts and the complete severing of the femoral artery and vein. The purpose of this study was to compare the effectiveness of four hemostatic agents to standard gauze (SG) dressing in a noncavitary, limited access, uncontrolled hemorrhage swine model. We hypothesized that, when compared to SG, hemostatic agents CG, WS, CF, and CA would significantly improve initial hemostasis, reduce incidence of rebleeding, and increase survival.

## METHODS

### Study Design

This was a laboratory study with swine. It was approved by the Naval Medical Center, Portsmouth, Virginia, Institutional Review Board/Institutional Animal Care and Use Committee (IACUC) protocol (CIP #P08–045). This research was conducted in compliance with the Animal Welfare Act and adhered to the principles stated in the National Institutes of Health Guide for the Care and Use of Laboratory Animals.[21] Protocol NMCP-08-045 was approved by the IACUC.

### Animal Subjects

Animals were maintained in a facility accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International. This study was conducted in the controlled environment of a veterinary surgical suite, accommodating up to four subjects simultaneously. Yorkshire swine (*Sus scrofa*, Blackwater Farms, Franklin, VA; 43.0 ± 7.7 kg) were chosen because of the species' reliability as a human cardiovascular model. Swine were fed a standard diet and observed for a minimum of 5 days to ensure good health. Eighty-nine swine were used: eight for the pilot training study, one was eliminated because of procedural error (incomplete transection of the femoral vessels), and the remaining 80 swine were included for statistical analysis based on the principle of intention to treat.

All animals were healthy. No animals were excluded prior to commencement of the study based on objective exclusion criteria. No animals exhibited outward signs of disease, such as elevated temperature, pulmonary findings, significant secretions on intubation, or other significant illness as determined by the attending veterinarian. No animals were excluded based on initial mean arterial pressure (MAP). Both male and female animals were included. It was determined a priori that any animal found to have an incomplete transection of the femoral vessels on necropsy would be excluded from analysis.

Swine were fasted the night prior to the procedure, with water provided ad libitum. Due to the small size of our laboratory, animals were randomized in groups of eight (the maximum amount we can hold at any time)

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and a veterinary tech not involved in the study, and thus blinded to the study protocol and test material selection, randomly selected each animal the day of the study. After premedication with buprenorphine (0.025 mg/kg) and intramuscular injection of ketamine (20 mg/kg), general anesthesia was induced via facemask with isoflurane in oxygen. Animals were intubated, and maintenance anesthesia was set at 2%. The animal was allowed to breathe spontaneously on 21% oxygen administered from an MDS Matrx VMC small animal anesthesia machine (Matrx Medical, Orchard Park, NY) for the duration of the procedure. After supine placement on an operating table, the front legs were secured to provide stabilization. A rectal temperature probe provided continuous core body temperature monitoring. Subject temperature was maintained at 36 to 38°C with electric table warmers and blankets. After exposure via cut-down technique, the right carotid artery was cannulated with a 20-gauge catheter for continuous arterial blood pressure monitoring. The right external jugular vein was cannulated with a 20-gauge catheter for infusion of resuscitative fluid. A Philips MP50 IntelliVue monitoring system (Philips Medical Systems, Böblingen, Germany) was used for continuous monitoring of vital parameters, including heart rate, MAP, oxygen saturation, core body temperature, and respiratory rate.

### Study Protocol

***Test Material.*** Four hemostatic dressings were compared to the control dressing, rolled Kerlix (Tyco Healthcare Group LP, Mansfield, MA) SG. CG, CF, and WS were purchased from their distributors. SAM Medical Products provided CA as part of a complete, unrestricted research grant. Table 1 summarizes the composition, mechanism of action, formulation, and application of these hemostatic agents.

The CG (Z-Medica Corporation, Wallingford, CT) is a nonwoven, rolled, medical gauze impregnated with kaolin, an activator of the intrinsic pathway of coagulation, tested by the Naval Medical Research Center[17] and the U.S. Army's Institute of Surgical Research[22] with encouraging results.

WoundStat (TraumaCure Inc., Bethesda, MD) is mineral-based granular smectite. Granules exposed to blood absorb water to form a malleable clay material with strong tissue adhesiveness. Additionally, the anionic nature of the material activates the intrinsic pathway to accelerate clot formation.[10,15,18]

Chitoflex (HemCon Inc., Portland, OR) is a chitosan dressing manufactured as a long, thin flexible wafer rolled into a product that can be placed into the wound in a manner similar to gauze. Once exposed to blood, chitosan acts by cross-linking red blood cells and platelets to form a mucoadhesive physical barrier around the site of hemorrhage. CF replaced HemCon, a rigid wafer pad with chitosan on only one side of the product. CF is thinner and more gauze-like, with chitosan on both sides of the product.

Celox-A (SAM Medical Products, Newport, OR) is the original Celox powder in a syringe-like applicator, specifically designed to deliver the agent directly to the deepest portion of a small, penetrating wound. Its mechanism of action involves the cross-linking of red blood cells and platelets to form a barrier and, like CF, is independent of the coagulation cascade for hemorrhage control.

***Pilot Study.*** A pilot study using eight swine was conducted to standardize procedural methodology across four participating surgeons. Each investigator gained familiarity with the procedural steps and practiced using the hemostatic agents as many times as necessary to achieve a high level of comfort with each phase of the experiment. The original surgical preparation model was developed by Gustafson et al.[23] and then validated at our institution in a previously published trial.[19] For the present study, two model changes were employed. Bleeding time was increased from 30 to 45 seconds, and the application of a pressure dressing after application of the agents was eliminated to better test the pure hemostatic efficacy of the test materials. These model changes to increase severity were specifically designed to ensure sufficient mortality to adequately test survivability between treatment groups. By participating in both the surgical treatment procedures and the observations of these procedures across eight swine, at the end of the pilot study, the four surgeons were well cross-trained in the standardized procedural steps for creating the wound, applying treatment, collecting data, and caring for the animal across the experimental design timeline (Figure 1).

Table 1
Hemostatic Agents: Composition, Mechanism of Action, Form, and Application

| Test Material | Composition | Mechanism of Action | Form | Application |
|---|---|---|---|---|
| CG | Kaolin impregnated rolled gauze | Activates intrinsic pathway of coagulation | Gauze 3 in. by 12 ft. | Packed into wound |
| WS | Smectite (nonmetallic clay) | Adsorbs fluid to form clay material. Activates intrinsic pathway | Granular agent; 5.5 ounces | Forms clay when wet which is packed into wound |
| CF | Chitosan | Cross-links red blood cells to form mucoadhesive bandage | Flexible rolled bandage 4 in by 4 ft. | Packed into wound |
| CA | Chitosan | Cross-links red blood cells to form mucoadhesive bandage | Granular agent; 0.2 oz. per tube | Two injectors place product deep into wound |

CA = Celox-A; CF = ChitoFlex; CG = combat gauze; WS = WoundStat.

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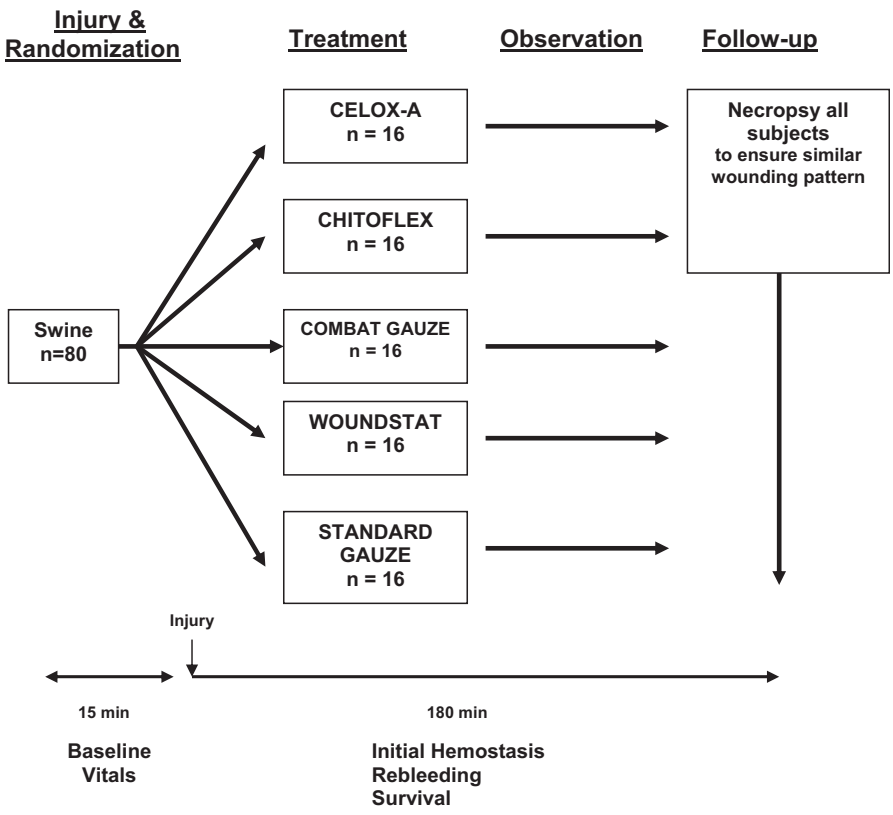


**Figure 1.** Experimental design timeline.

***Vessel Exposure.*** The simulated linear tract projectile wound was created along the right inguinal crease by first creating a 3.0-cm incision in the skin of the medial thigh using a No. 10 blade scalpel. The femoral artery was exposed via conservative digital dissection and discerned by palpation of the femoral pulse. Direct manipulation and exposure of the femoral vessels was avoided. A linear tract was then created by perforating the quadriceps with 8-inch Rochester-Carmalt forceps, approximately 1.5 cm lateral to the femoral artery at its most superior aspect near the inguinal ligament. The forceps were placed in the skin incision superficial to the femur and deep to the rectus femoris. The instrument was advanced through the vastus medialis, through the vastus intermedialis, and exited through the vastus lateralis. The exiting skin wound was enlarged with a No. 10 blade scalpel to a total length of 10 cm. The quadriceps tract was enlarged by spreading the forceps inside the tract and by digital manipulation. A portion of rolled gauze bandage (Kerlix) was advanced through the wound and used to roughen the edges of the tract. The goal of this injury design was to simulate the ragged, lacerated muscle of the cavity associated with high-velocity projectile tracts.

***Baseline Vital Signs.*** Animals were allowed a stabilization period of 15 minutes after wound tract creation and prior to creation of the vascular injury. Vital signs were closely monitored during this baseline period. Anesthesia was decreased to 1% gradually during this stabilization period, titrated to adequate surgical pain threshold, as determined by motor response to hoof and corneal stimulation.

***Wounding.*** At the end of the 15-minute stabilization period, a complex injury with complete transection of the femoral artery and vein was created through the 3-cm skin incision. The femoral arterial pulse was palpated with an index finger through the 3-cm incision. The femoral neurovascular bundle was then completely transected approximately 2 cm distal to the inguinal ring using a No. 20 blade scalpel, so the artery could bleed freely for 45 seconds before treatment was applied.

***Hemostatic Treatment.*** Prior to application of hemostatic agents, animals were randomly assigned to one of five treatment groups (SG, CF, CG, WS, CA; $n = 16$ each). Our randomization method was placing each test material on 16 cards for a total of 80 cards and then shuffling these cards 10 times to achieve adequate randomization. Cards were then selected in subsequent order from the deck. Treatment was applied immediately following the 45-second hemorrhage. Each agent was applied in strict adherence with the instructions provided by the manufacturer. The surgeon who made the injury applied the agent. The nongranular agents SG, CF, and CG were applied by briskly inserting the dressing directly into the wound, unrolling the bandage as it was inserted. As much of the dressing was packed into the wound as was possible. Following insertion, a rolled gauze bandage was used to pack the remainder

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of the wound and then positioned on top of the wound opening, and direct manual pressure was applied to the dressing.

WoundStat was applied by first wiping the opening of the skin incision clear with standard 4 × 4-inch gauze (Curity, Tyco Healthcare Group LP, Mansfield, MA) and then pouring the contents of one package of agent into the wound and manually packing as much agent as possible through the bleeding and into the wound in accordance with the manufacturer's instructions. A rolled gauze bandage was inserted in the remainder of the wound if room allowed and then placed over the top, followed by pressure with the nondominant hand for 5 minutes.

Celox-A was applied by placing the injector apparatus as far into the wound as possible and injecting the agent rapidly. This was performed with two applicators in accordance with the manufacturer's recommendations. Rolled gauze was used in a similar manner as for all the other agents.

In all cases, consistent manual pressure was applied for 5 minutes. Any bleeding that occurred in the first 5 minutes after release of this pressure was considered a failure of initial hemostasis.

***Observation Period.*** Measurements of heart rate, MAP, respiratory rate, oxygen saturation, and temperature began 15 minutes prior to the injury and continued at 5-minute intervals until 180 minutes had elapsed or death occurred (total 195-minute observation time). Fluid resuscitation was initiated 10 minutes postinjury with 500 mL of 6% hetastarch in 0.9% sodium chloride solution (HESPAN, B. Braun Medical Inc., Irvine, CA), infused via a right external jugular vein intravenous line over a period of 30 minutes, consistent with previous studies in this model.

***Postmortem Analysis.*** Each animal received limited necropsy upon expiration. Local inspection of the wound was used to verify complete transection of the femoral vascular bundle, evaluate appropriate placement of the agent, and identify the presence of any hematoma that had formed. Full necropsy was performed on animals that expired without visible evidence of rebleed or large hematomas to evaluate for any comorbid illnesses or unforeseen procedural error. One animal was excluded due to investigator error in creation of the vascular injury. This animal's femoral vessels were incompletely transected. Therefore, data obtained from this animal were excluded from data analysis in accordance with our a priori study design. All 80 animals included for statistical analysis were determined to be free from any complication or surgical error during necropsy examination.

**Measurements**

The primary outcome measures were failure of initial hemostasis and incidence of rebleeding. Secondary endpoints included total blood loss, amount of rebleeding, and survival. Blood was collected into preweighed collection canisters by suctioning the area around the wound during hemorrhage. Preweighed plastic bags were positioned beneath the animal's hindquarters to accommodate blood that was not contained by the suction device. Dressings, hemostatic agents, and table liners were weighed before and after the experiment, with the difference added to the collected blood to sensitively estimate initial blood loss.

Bleeding that occurred after the first 5 minutes following pressure release was considered a rebleed. Once fluid resuscitation began, a second fresh plastic bag was placed beneath the animal to collect any blood loss from rebleeding. This took the form of external bleeding or the development of a hematoma within the wound. External rebleeding was defined as blood that oozed visibly from around the dressing; this blood was suctioned into a separate canister or collected in the second plastic bag to determine quantity. Hematomas were defined as well-circumscribed collections of clotted blood within the wound cavities and surrounding tissues evident upon necropsy. Any hematomas were removed at the end of the experiment and weighed separately. Care was taken to avoid contamination of the blood with other body fluids and solids.

Death criteria were apnea and/or loss of the MAP tracing for 10 continuous minutes. Subjects that survived through 180 minutes of observation were euthanized with an intravenous injection of sodium pentobarbital solution (Euthasol, Virbac Animal Health, Inc., Ft. Worth, TX).

**Data Analysis**

Sample size determination was based on previous published reports and statistical tests of power. Previously published studies of hemostatic testing in swine have commonly ranged from 7 to 12 per group.[9,11–13,15–17,19] Tests of power revealed that, with an effect size of 0.5 standard deviations at a threshold of $p < 0.05$, statistically significant differences would be realized 70% of the time (power = 0.70) with as few as 11 per group in omnibus one-way analysis of variance (ANOVA) testing, and with as few as 13 per group to localize effects. To account for the possibility of high variability or unforeseen complications in this severe hemorrhagic model, the present study included a sample size of $n = 16$ per group, $N = 80$ total.

Body weights, pressures, and blood loss data were analyzed using between-groups ANOVA, with pairwise comparisons using Fisher's least squared differences to localize statistically significant effects. To guard against violations of ANOVA assumptions, each ANOVA result was confirmed by the nonparametric Kruskal-Wallis test and localized using the Mann-Whitney U-test. The crucial independence assumption of ANOVA was fostered by using shuffled card selection to ensure random assignment of swine to treatment groups. Log expressions reduced skew in total bleed to nonsignificant levels, while a square expression of peak MAP corrected for significant negative skew and a square root expression of prebleed brought significant skew and kurtosis to nonsignificant levels. Significant positive skew and kurtosis were evident in rebleed regardless of transformation because the modal value was zero, but a 1-padded log expression of rebleed was determined to be the optimal expression to ameliorated skew and kurtosis. For these reasons, it was particularly important to

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analyze and interpret rebleed as a yes–no binary variable in addition to ANOVA analyses. ANOVA F- and p-values reflect transformed expressions, but to enhance readability and interpretation, all variable descriptives included in text, tables, and figures reflect untransformed values. Data were organized, checked for errors, and analyzed using Microsoft Excel (Microsoft Corp., Redmond WA) and SPSS (SPSS Inc., Chicago IL).

Categorical data, including initial hemostasis, incidences of rebleeding, and survival were contrasted first using overall chi-square analysis and then with binomial statistics to localize significant effects between groups. To balance the concerns for alpha inflation from multiple comparisons (type I error) and missing important differences (type II error), the statistical significance threshold was set at $p < 0.01$ for all comparisons.

## RESULTS

There were no statistical differences between groups in body weight or preinjury vital parameters, including pretreatment MAP (pre-MAP) and peak MAP, $F(4,75) < 1.0$ (Table 2).

### Failure to Achieve Initial Hemostasis

Overall, 15% of participants (12 of the 80) failed to achieve initial hemostasis (success rate = 85%). Initial hemostasis was not significant by overall chi-square analysis ($\chi^2 = 7.5$, df = 4, $p = 0.11$), but localizing binomial comparisons revealed that WS (31%, 5/16) was significantly higher in initial hemostasis failure rate than CA (5/16, 31% vs. 0/16, 0%; $p < 0.002$); other comparisons were not significant (Table 3).

### Incidence of Rebleeding

Overall rate of rebleeding was 33% across groups. Incidence of rebleeding was not significantly different between groups ($\chi^2 = 5.4$, df = 4, $p = 0.25$). The incidence of rebleeding appears higher in CF (9/16, 56%) than in CA, CG, and WS (each 4/16, 25%), but these differences were not statistically significant at the preselected 0.01 threshold ($p = 0.02$, binomial test; Table 3).

### Survival and Mortality

Overall mortality prior to 180 minutes was 24% across groups. Mortality was not significant by overall chi-square analysis ($\chi^2 = 5.1$, df = 4, $p = 0.28$), but localizing binomial comparisons revealed that mortality in WS (44%, 7/16) was significantly higher than mortality in CA (7/16, 44% vs. 2/16, 13%; $p < 0.01$); other comparisons were not significant (Table 3).

### Blood Loss

No statistically significant differences were detected between groups in preresuscitation blood loss, amount of rebleeding, or total blood loss ($p > 0.05$, ANOVA and Kruskal-Wallis). WS (35.7 mL/kg; 95% confidence interval [CI] = 28.6 to 42.7) appeared to be somewhat higher than CA (26.6 mL/kg; 95% CI = 20.1 to 33.1) in total blood loss, but this difference failed to achieve statistical significance at the preselected 0.01 threshold ($p = 0.05$; Table 4, Figure 2).

## DISCUSSION

### SG Performed as Well or Better Than the Hemostatic Agents

Perhaps the most surprising finding of the present study was that SG performed similarly to most hemostatic agents across all outcome measures, even though the experimentally induced wound was specifically designed to challenge survival.

Gauze likely provides a mesh of fibers for coagulation to occur, particularly in a noncavitary model, which provides a natural tamponading effect from the surrounding tissue. But in cases of uncontrolled bleeding from the femoral artery, no gauze or presently known hemostatic agent will prevent mortality without the fundamentals of proper wound packing and pressure application.

A recent study in our laboratory showed the equivalence of SG to other hemostatic agents in a severe hemorrhage model, wherein wound packing, pressure, and a pressure bandage left on for the duration of the study led to excellent hemorrhage control regardless of the agent used.[19] SG survival rate was 81% in the present study, even though direct pressure was applied for only 5 minutes and no pressure dressing was used. The present findings with respect to SG highlight that the historical principles of adequate wound packing and pressure form the foundation of hemorrhage control and subsequent survival.

### CA Was Superior to WS in Initial Hemostasis and Survival

Hemostasis normally begins with platelet aggregation and formation of a platelet plug, providing a foundation

Table 2
Animal Weights and Arterial Pressures

| Group | Statistic | CA | CF | CG | SG | WS |
|---|---|---|---|---|---|---|
| Weight (kg) | Mean/median | 40.2/40.3 | 40.3/40.9 | 40.2/38.9 | 38.2/38.7 | 39.3/40.0 |
| | 95% CI | 36.1–44.3 | 37.7–43.3 | 36.7–43.7 | 35.5–40.9 | 35.7–42.8 |
| Pre-MAP | Mean/median | 64.6/64.5 | 72.5/71.0 | 72.6/74.6 | 68.2/68.5 | 63.9/63.0 |
| | 95% CI | 58.8–70.4 | 63.2–81.8 | 64.4–80.9 | 61.3–75.0 | 57.9–69.9 |
| Peak MAP | Mean/median | 57.4/57.5 | 56.4/58.0 | 58.3/60.0 | 58.2/60.5 | 50.8/52.0 |
| | 95% CI | 51.0–63.9 | 45.6–67.1 | 47.4–69.2 | 50.2–66.2 | 41.5–60.2 |

CA = Celox-A; CF = ChitoFlex; CG = combat gauze; MAP = mean arterial pressure; SG = standard gauze; WS = WoundStat.

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Table 3
Initial Hemostasis, Rebleed, and Survival

| | | Initial Hemostasis | | Rebleed | | Survival | |
|---|---|---|---|---|---|---|---|
| Group | *n* | Yes | % | Yes | % | Yes | % |
| CA | 16 | 16 | 100 | 4 | 25 | 14 | 88 |
| CF | 16 | 13 | 81 | 9 | 56 | 13 | 81 |
| CG | 16 | 15 | 94 | 4 | 25 | 12 | 75 |
| SG | 16 | 13 | 81 | 5 | 31 | 13 | 81 |
| WS | 16 | 11 | 69 | 4 | 25 | 9 | 56 |
| Total | 80 | 68 | 85 | 26 | 33 | 61 | 76 |

CA = Celox-A, CF = ChitoFlex, CG = combat gauze, SG = standard gauze, WS = WoundStat.

for a thrombus to then form after initiation of the coagulation cascade. CA may offer an advantage by initiating a barrier of cross-linked red blood cells immediately, prior to (or simultaneous with) platelet aggregation. CG and WS both activate the coagulation pathway, a later step in the process of hemostasis, and this may put them at a disadvantage in the immediate control of hemorrhage—particularly in the face of coagulopathy from severe hemorrhagic shock. However, CA proved superior only to WS with respect to initial hemostasis and survival.

The original formulation of Celox granules (CX), which are poured directly on the site of hemorrhage, were previously found to be not superior to WS with respect to initial hemostasis (CX 7/10, WS 6/10) in an open wound punch model,[15] possibly because WS is molded to the geometry of an open wound to form a physical barrier. In the present limited access model, the applicator form of CA was convenient and generally superior in localizing the agent when compared to pouring and packing WS into a small wound, but the applicator tube size was determined by the manufacturer to be insufficient without two tubes of agent. One misapplication error with CA was detected postmortem, with one of two tubes of agent missing the target. This animal performed similarly to other surviving animals, with no initial hemostasis failure or rebleed, and was included in the study based on the principle of intention to treat. It seems probable that the main reason this subject did not rebleed was the fact that all subjects underwent firm wound packing after the application of agent. To reduce error due to the need for double applications, a larger volume CA applicator may be as effective while being easier to apply.

Our research group previously found no difference in the original CX powder when compared to SG in outcomes using a model similar to that used in the present study.[19] However, a pressure dressing was used throughout the entire observation period in the previous trial. This highlights the fact that adequate wound packing is probably even more important than the application of a pressure dressing, particularly in anatomical areas where pressure dressings are difficult, such as the groin or axilla.

### Rebleeding Rates Were Comparable Across Agents

Rebleeding occurred in the CF group at twice the rate of other groups, but this was not a statistically significant difference. While CA and CF are both chitosan-based and form a physical barrier by cross-linking red blood cells, the performance of CA in initial hemostasis and rebleeding may be because a granular product conforms readily to the geometry of a wound, while a flexible wafer does not. Additionally, CF has to be folded multiple times to treat limited access wounds and thus does not provide a continuous interface with injured vessels.

Chitosan wafers (Hemcon) do work well in low pressure models when there is no pool of blood.[24] In high-pressure models, these wafers tend to break down over time and rebleeding ensues.[10,16,25] Because chitosan dressings rely on mucoadhesion, they are subject to the physical force of rising blood pressure during resuscitation. The present study used the dual sided CF, but showed similar rebleed trends as the original HemCon formulation.

Combat gauze did not outperform the other agents in this study. This is similar to a recent study of CG (then termed X-sponge), WS, SG, and CX where all performed similarly with respect to initial hemostasis, post-treatment blood loss, and survival.[16] However, in an arterial punch model, CG outperformed CX in initial hemostasis and survival.[23] In this study the version of CX used was the original powder inside a bag that dissolves when in contact with blood. The mechanism by which CX confers hemostasis is thus delayed while the bag dissolves, likely decreasing its ability to obtain initial hemostasis.

In our limited access model, it anecdotally did take notably more time to apply CG than the other agents prior to placing definitive manual pressure. This

Table 4
Blood Loss

| Group | Statistic | CA | CF | CG | SG | WS |
|---|---|---|---|---|---|---|
| Prebleed | Mean/median | 22.6/23.5 | 24.5/25.7 | 26.3/25.8 | 27.4/26.2 | 25.9/23.4 |
| | 95% CI | 18.8–26.3 | 19.8–29.2 | 20.2–32.3 | 22.9–32.0 | 21.7–30.1 |
| Rebleed | Mean/median | 4.0/0 | 6.3/4.1 | 6.7/0 | 4.6/0 | 9.8/0 |
| | 95% CI | 0–8.6 | 2.6–9.9 | 0.8–12.5 | 0.4–8.8 | 2.1–17.4 |
| Total bleed | Mean/median | 26.6/25.6 | 30.7/29.8 | 32.9/27.6 | 32.0/27.1 | 35.7/35.8 |
| | 95% CI | 20.1–33.1 | 23.6–37.8 | 24.0–41.8 | 24.0–40.0 | 28.6–42.7 |

CA = Celox-A, CF = ChitoFlex, CG = combat gauze, SG = standard gauze, WS = WoundStat.

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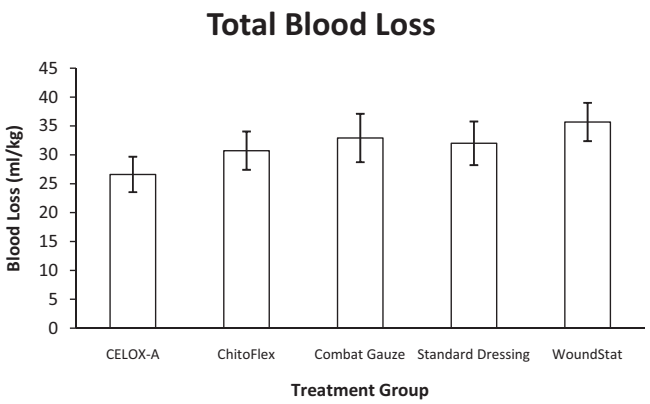


**Figure 2.** Total blood loss by group. Note: Error bars indicate standard error of the mean.

occurred because CG comes as a 12-foot roll of material. In open wounds, decreased blood loss is obtained by maintaining pressure over the source of hemorrhage while packing the wound. We were unable to adequately visualize the source of bleeding, thus allowing continuing hemorrhage to occur, increasing the overall blood loss in the CG arm.

### WS Showed a Lower Rate of Initial Hemostasis and Higher Mortality When Compared to CA

The WS rate of survival in this study was only 56%. This finding conflicts with evidence from previous studies where this product performed remarkably well. This may be due to the differences in the models used, the application, or the intrinsic properties of WS.[10,15–18]

Our limited access model did not provide visualization of the bleeding vessels. This is important because WS did not have a delivery mechanism similar to CA. However, WS was designed to be applied through a pool of blood, absorbing moisture to form a clay material while simultaneously activating the coagulation pathways. It is then manually packed and molded into the wound. We hypothesized that the nature of the wound would not be a limiting factor for WS. While we were able to mold over half of the 5.5-ounce material in the WS package into the wound, this lack of visual access of the source of bleeding likely resulted in the increased failure of initial hemostasis and resulted in excessive blood loss, which increased mortality.

Because WS absorbs fluid to form a malleable clay material, this may require a second application of molding to confer hemostasis in an open wound. Subsequent studies on WS were designed in this manner. However, our judgment in designing the limited access model, and in testing hemostatic agents in general, is that obtaining initial hemostasis is absolutely critical in improving outcomes in the face of uncontrolled hemorrhage. This is particularly important in military operations where multiple casualties and delays to definitive care mean that every ounce of blood is critical.

Further, there were two unexplained deaths early after the initial injury in WS subjects. These animals, while maintaining heart rate and blood pressure, lost spontaneous respirations during the resuscitation phase. Both cases occurred approximately 15–20 minutes after wounding. These animals were included based on the principle of intention to treat. While host response to the injury itself could have caused early death, this is unlikely because these two animals were similar to others in the volume of pretreatment hemorrhage and in all baseline parameters. While our limited postmortem necropsy was not designed to identify thromboembolic events, it is possible that pulmonary embolism from WS could have caused these deaths.[26] Embolization could be more frequent with WS, which requires firm packing and molding into the wound, as opposed to granular agents such as CX or Quikclot, which require only application and pressure. Due to safety concerns over embolization and tissue inflammation, the Committee on Tactical Combat Casualty Care (TCCC) removed WS from its guidelines as of February 2009.

### Practical Implications for the Practitioner

In extremity trauma, rapid and effective hemorrhage control is key to increasing survival, particularly in combat situations where there are simultaneous casualties in a compressed time frame with inherent delays to definitive care. Other than WS, there were no differences among the agents tested. Therefore, SG can be recommended as strongly as the hemostatic agents CA, CG, and CF for the treatment of small penetrating extremity injuries with severe vascular trauma.

There were important observations concerning the actual application of the four agents. All agents were easily removed from their packaging and prepped for use during the 45 seconds of uncontrolled hemorrhage. CF was easily inserted into the wound while bleeding continued, but due to the adhesive nature of the product, if it was not unrolled completely the roll would become ''glued'' together upon contact with blood. Therefore, we recommend completely unrolling the product prior to insertion. CG is thin and lengthy (12 feet) when compared to CF, taking longer to fully pack into the wound. This allowed for continued bleeding during the 45–60 seconds it took to place the product into the wound. Therefore, it took longer to establish initial manual pressure when compared to the other products. WS is a granular material designed to be packed through a ''pool of blood.'' While this was more difficult in a smaller wound, it was accomplished with over half of the 5.5-ounce material in less time than with CG. Although there were more frequent failures in initial hemostasis with WS than with CA, we did not attempt a second application. A second application after initial failure is a component of the three prior studies utilizing WS. However, the ability to achieve initial hemostasis quickly is an important criterion for a hemostatic agent in far-forward environments with delay to definitive care. CA injectors were easily placed into a 3-cm wound but the need to use two did lead to more time before the placement of definitive manual pressure, thus slightly increasing hemorrhage volume. When analyzing the product on necropsy, it was found that there was unused agent remaining in the wound after the achievement and maintenance of hemostasis. We conjecture that the production of a single injector

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with increased volume may be a more favorable formulation.

## LIMITATIONS

Our group previously published a trial of hemostatic agents using the traditional large inguinal wound.[12] Some operational medical providers felt this efficacy model was too artificial and did not reflect actual battlefield conditions. Specifically, its large cavitary wound permitted easy visualization of the bleeding vessel, allowing investigators applying the agent to place the agent directly on the bleeding site with certainty. Reflecting military operational input, our next trial utilized Gustafson's limited access model,[23] preventing direct visualization of the bleeding site and adding the challenge of proper placement of the agent. However, we modified Gustafson's model with the addition of pressure dressing placement.[19] This model failed to identify differences between agent effectiveness, leading us to conclude that the proper and continuous application of pressure may be the more important management variable for treatment of these limited access wounds. When designing the current trial, we removed the use of the pressure dressing to focus primarily on the hemostatic effects of the agent. This reversion back to the absence of a pressure dressing removes this potential confounder, but moves the experimental design away from actual field treatment of complex groin injury. Therefore, any treatment effect differences identified in our current trial, and any efficacy trial, will likely overestimate the effective hemostatic differences between agents when they are used in conjunction with accepted field wound management principles such as wound packing, pressure dressing application, and damage control resuscitation. However, as previously stated by Kheirabadi et al.,[22] if an agent achieves hemostasis in these efficacy models, it should perform at least as well under field conditions. This has implications when making recommendations to civilian EMS directors, military medical providers, and acquisition experts regarding complete replacement of recommended hemostatic agents with new agents. Efficacy trials can identify the best agent, but are limited in identification of how much better the agent will perform in the prehospital setting.

The present model attempts to approximate a penetrating injury with a small entrance wound, complete severance of artery and vein with concomitant muscular injury, and a large exit wound. In actual wounds of a similar nature, the amount of secondary tissue injury and inflammation is much greater due to the ballistic nature of the injury mechanism. Our model cannot recreate this type of secondary tissue damage. We have previously suggested that only a true ballistic model of complex groin injury can reproduce a truly faithful combat injury.[27]

The nature of a complete transection injury invites variability in pretreatment blood loss when compared with arterial punch models. The pretreatment hemorrhage ranged from 9.2 to 44.8 mL/kg in our study, without significant differences between the groups. While this variability in pretreatment hemorrhage may be from vasospasm or vessel retraction that differs individually by subject, it may also be secondary to variability introduced by the investigator conducting a blind transection based solely on the ability to palpate the femoral pulse. Overall, we doubt that vasospasm is a limiting factor. Not only was the hemorrhage more severe than 6-mm arteriotomies, difficulty with initial hemostasis and rebleeding remained a problem for the majority of agents throughout the study.

Unlike some investigators of hemorrhagic shock, we did not splenectomize our subjects. Our aim was not to test a hemodynamic response. We have investigated hemostasis using a physiologic model selected to test an agent's efficacy in improving survival under conditions and variables that are encountered in the field. The need for splenectomy has likewise come into question in hemostatic agent studies because the current practice of replacing the spleen volume with three times its weight in crystalloid may produce a baseline dilutional coagulopathy that would confound the results. Until the effects of splenectomy in swine can be better characterized, we advocate that it should no longer be used in standard hemorrhagic models.[28]

A MAP of less than 60 mm Hg was not an exclusion criterion in our study. However, the MAP average at baseline prior to injury and after anesthesia was 71 mm Hg (Figure 3).

The resuscitation protocol was an attempt to simulate the most rapid response of a prehospital provider. The hemorrhage time was 45 seconds followed by application of the agent and manual pressure with the nondominant hand for 5 minutes. This simulates the condition of a responder or provider holding pressure with one hand while attempting to continue working on the scene with the other. Resuscitation began at 10 minutes after pressure was released (15 minutes postinjury), which is about as quickly as a prehospital medical provider might be able to get intravenous or intraosseous access under field conditions.

We did not resuscitate to a target MAP. This would not be a realistic scenario in the field. Instead, we attempted to follow TCCC recommendations of colloid use for initial resuscitation. Using a standard volume of resuscitative fluid in a bolus fashion better approximates prehospital practices. TCCC recommends a bolus of 500 mL of Hextend if the systolic blood pressure is less than 80 mm Hg in a human subject, corresponding to onset of altered mental status or a nonpalpable or weak radial pulse.[29]

We used Hespan rather than Hextend as our resuscitative fluid. Hespan was readily available for our laboratory, whereas Hextend was not. There is evidence that Hespan may exacerbate coagulopathy when compared to Hextend,[30] and Hextend remains the resuscitative fluid of choice per TCCC recommendations. In addition, intravenous fluids that are not blood products will dilute clotting factors and lower the pH. Both of these situations prevent the body's clotting mechanism from working optimally. Fluids can also lead to the exacerbation of hypothermia so common in massive trauma, leading to further dysfunction of the enzymes involved in the coagulation cascade. By raising the blood pressure artificially with overresuscitation,

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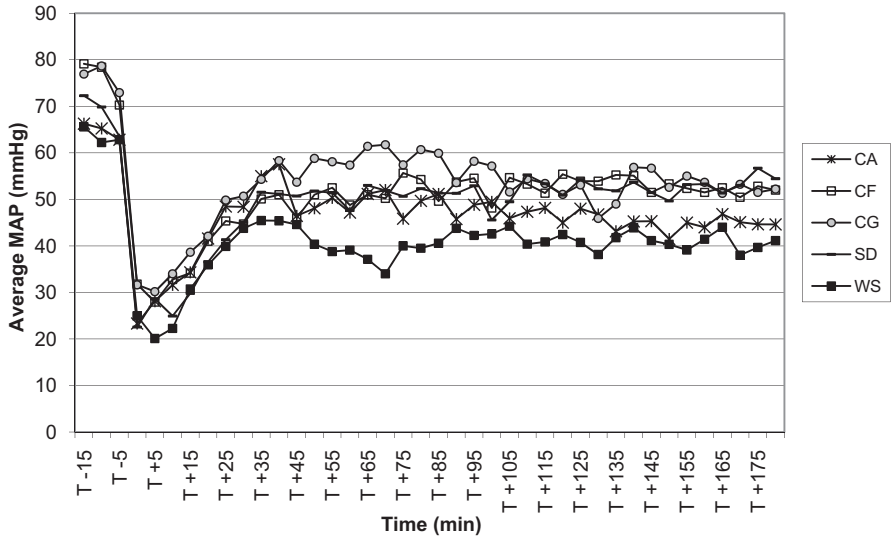


**Figure 3.** Mean arterial pressure over time. CA = Celox-A; CF = ChitoFlex; CG = combat gauze; SG = standard gauze; WS = WoundStat.

the initial soft thrombus that is formed to stop hemorrhage is disrupted and further hemorrhage ensues. Therefore, our model used a single bolus of Hespan to parallel field conditions, rather than a fixed target MAP.

### Areas of Future Research

Studying hemostatic agents is challenging because injury patterns differ, and hemostatic agents differ in both the mechanism of action and the material form. The present study found that gauze-type agents and granular agents with delivery mechanisms were more efficacious. However, a ballistic model with a large exit wound may prove useful for replicating gunshot wounds and shrapnel from improvised explosive devices. No such model exists that would provide a consistent wounding pattern. Since replication of the wound is the most difficult part of developing such a model, the use of ultrasound-guided vessel marking may be required for validation. Ultimately, we need models that match the trauma seen in prehospital settings before reaching definitive conclusions regarding the optimal material form of hemostatic agents.

Effects of training are unknown. Hemostatic agents may be efficacious in the hands of experienced researchers and clinicians, but little is known regarding the relationship between skills training and the efficacy of hemostatic agents. Improper application of hemostatic products by novice users may jeopardize outcomes, so as products develop, tracking the usability by novices and determining appropriate training assessment are important areas for future research. The findings with respect to SG indicate that the most important part of training for the emergency medical technician, the combat lifesaver, and the medic and corpsman is proper wound packing and pressure.

Coagulopathy presents challenges for standard techniques in treating severe hemorrhage. Hemostatic agents should be investigated regarding both the early coagulopathy found in severe trauma and in patients on anticoagulants such as warfarin or heparin. Because many hemostatic agents rely on a normal functioning coagulation system, it is important to develop agents that confer benefit in cases of trauma with coagulopathy.

## CONCLUSIONS

Standard gauze dressing was as efficacious as Celox-A, Chitoflex, and combat gauze in treating uncontrolled hemorrhage from small penetrating wounds not amenable to tourniquet placement. The present findings also suggest that the form factor of poured granules may not be as effective as tube-delivered hemostatic granules or gauze products in the present model specifically designed to simulate the ragged, lacerated muscle of the cavity associated with high-velocity projectile tracts and the complete severing of the femoral artery and vein.

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